A STUDY ON ASSESSMENT OF CARDIAC FUNCTION IN NON DIABETIC NON SMOKER CHRONIC KIDNEY DISEASE

Dissertation submitted for

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2011

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY
Chennai - 600 032

MADURAI MEDICAL COLLEGE, MADURAI

CERTIFICATE

This is to certify that this dissertation titled *"**A STUDY ON ASSESSMENT OF CARDIAC FUNCTION IN NON DIABETIC NON SMOKER CHRONIC KIDNEY DISEASE"*** submitted by **Dr.P. BALAMANIKANDAN** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

DR.C. DHARMARAJ, M.D.,
PROFESSOR AND UNIT CHIEF,
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE,
MADURAI.

DR.MOSES K. DANIEL, M.D.
PROFESSOR AND HEAD,
DEPARTMENT OF MEDICINE
MADURAI MEDICAL COLLEGE,
MADURAI.

DECLARATION

I**, DR.P.BALAMANIKANDAN,** solemnly declare that the dissertation titled "***A STUDY ON ASSESSMENT OF CARDIAC FUNCTION IN NON DIABETIC NON SMOKER CHRONIC KIDNEY DISEASE"*** has been prepared by me. This is submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date: **Dr.P. BALAMANIKANDAN**

ACKNOWLEDGEMENT

At the outset, I wish to thank our Dean **Dr. EDWIN JOE M.D.,** and Medical Superintendent **Dr.S.M.SHIVAKUMAR, MS**, for permitting me to use the facilities of Madurai Medical college and Government Rajaji Hospital to conduct this study.

I wish to express my respect and sincere gratitude to my beloved teacher and Head of Department of Medicine **PROF.Dr.MOSES K DANIEL M.D and to former H.O.D OF MEDICINE PROF.DrA.AYYAPPAN M.D** for their valuable guidance and encouragement throughout the study and also during my post graduate course, I owe my sincere thanks to them.

I also owe my sincere thanks to my beloved former unit chief and my guide **PROF.DR.D.D.VENKATRAMAN M.D.** and also to my unit chief **PROF.DR.C.DHARMARAJ M.D.** and I express my sincere thanks to **PROF. Dr.M.SHANMUGA PERUMAL M.D D.M** for their valuable guidance and support throughout the conduct of the study.

I express my special thanks to Asst professors. **Dr.G.SELVARANI M.D DHSc, Dr.P.S.ARULRAJAMURUGAN**

MD.DM, Dr.R.R.SARAVANAN M.D, Dr.S.SAKTHIMOHAN M.D., Dr.G.GURUNAMASIVAYAM M.D, Dr.KASI PANDIAN M.D for their excellent guidance throughout the study.

I profusely thank the **Department of Nephrology, Department of Cardiology and Department of Biochemistry** for their full cooperation and support.

My family and friends have stood by me during my times of need. Their help and support have been invaluable to the study.

Finally, I thank all the patients , who form the most integral part of the work, were always kind and cooperative. I pray for their speedy recovery and place this study as a tribute to them. Above all I thank the Lord Almighty for His kindness and benevolence.

DEDICATED TO MY BELOVED TEACHERS

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). CKD affects virtually every organ system of the body, resulting in an increase in morbidity and mortality.

Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. Emerging evidence indicates that the function of these two organ systems are affected by each other in a complex interplay. The incremental risk of cardiovascular disease in those with CKD compared to the age- and sex-matched general population ranges from 10- to 200-fold, depending on the stage of CKD. Between 30 and 45% of patients reaching stage 5 CKD already have advanced cardiovascular complications. As a result, most patients with CKD succumb to cardiovascular disease before ever reaching stage 5 CKD.

. Most patients with CKD suffer frequently from cardiac abnormalities including left ventricular hypertrophy (LVH), left ventricular dilatation (LVD), left ventricular (LV) diastolic and/or systolic dysfunction. Left ventricular hypertrophy(LVH) is one of the

strongest risk factors for cardiovascular morbidity and mortality in patients with CKD.

Hypertension is one of the most common complications of CKD. It usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. Uncontrolled hypertension accelerates the rapid worsening of cardiac function and results in more severe grades of left ventricular hypertrophy.

The cardiorenal syndrome, defined as the confluence of cardiac and renal impairment, has been recognized as a known entity in which not only do cardiac and renal dysfunction coexist, but the failure of one system accelerates the decline of the other.

The present study was aimed at assessing cardiac function in patients with varying stages of CKD in non diabetics and non smokers. Echocardiography is a simple and non invasive tool to assess LV mass and systolic and diastolic dysfunction in these patients. The study further assesses the effect of uncontrolled hypertension in these patients.

The study is aimed further in assessing the advent of Tissue Doppler Imaging (TDI) in assessing diastolic dysfunction as compared to

conventional echocardiography. The study further compares the different modalities of measurement of LV mass in these patients.

REVIEW OF LITERATURE

Chronic kidney disease is a pathophysiologic process with multiple etiologies existing for more than 3 months resulting in inexorable attrition of nephron number and function frequently leading to end stage renal disease (ESRD).

Chronic kidney disease (CKD) is a global threat to health in general and for developing countries in particular, because therapy is expensive and life-long. In India, ~90% patients cannot afford the cost.

The epidemiology of CKD in India is very different from the West. Patients are roughly two decades younger, and a substantial proportion present with small kidneys, so the aetiology of CKD is unclear[1]. The aetiology of these epidemiologic differences is unknown. Probably a correlation does exist between low birth weight and diminished nephron number[2].

In one study conducted by Charumathi Sabanayagam[3] concerning the ethnic disparities in CKD, it was found that older age and the presence of diabetes, hypertension and dyslipidaemia were significantly associated with CKD in all ethnic groups. Clinical,

metabolic, socioeconomic and behavioural factors accounted for 78% of excess risk of CKD in Indians. Hypertension contributes to 23% of greater population-attributable risk of CKD.

In another study, variations in Th1/Th2 regulatory lymphocyte balance and relationship to glomerulonephritis as postulated by the 'Hygiene hypothesis'[4] has been proposed as a contributing factor.

Another hypothesis proposed is the 'Asian Indian Phenotype' or 'Thrifty Phenotype' of truncal/visceral obesity and insulin resistance[5].

In one study conducted by All India Institute of medical sciences[6], the prevalence of CKD in India is ~0.8%. Diabetes has emerged as the most frequent cause (30–40%) followed by hypertension (14–22%), chronic glomerulonephritis (16–20%), chronic interstitial nephritis (5.4–12.7%), heredofamilial disease (8.4%) and obstruction including calculus (2.9%) .

In 2005, the Indian Journal of Nephrology adopted the National Kidney Foundation- Kidney Dialysis Outcome Quality Initiative (NKF-KDOQI)[7] and European Best Guidelines as a template to compile guidelines for management of CKD and pre-ESRD patients in India. For purposes of staging CKD, current guidelines recommend

two methods for measuring estimated glomerular filtration rate (eGFR). These include the Cockgroft Gault equation and equation from the modification of diet in renal disease (MDRD).

Cockgroft Gault equation :

$$\text{Creatinine clearance} = \frac{(140\text{-age}) \times \text{bodyweight (kg)}}{72 \times \text{S.creat (mg/dl)}} \times 0.85 \text{ (for women)}$$

MDRD formula :

The Modification of Diet in Renal Disease (MDRD) study was a multicenter, controlled trial that evaluated the effect of dietary protein restriction and strict blood pressure control on the progression of renal disease. From this study, it was determined that older age and female sex were independent predictors of GFR, reflecting the well-known relation of age and sex to muscle mass. GFR was further adjusted for body surface area so that neither height nor weight was an independent predictor of adjusted GFR. African American ethnicity was an independent predictor of higher GFR as on average, black persons have greater muscle mass than whites.

Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

Multiply by 0.742 for women, Multiply by 1.21 for African Americans

There are some limitations of this calculated GFR. It may not be accurate if kidney function is fluctuating and not in a steady state or in cases where muscle mass is abnormal. The GFR estimate may be inaccurate in extremes of age and in patients with severe malnutrition or obesity, paraplegia or quadriplegia, and in pregnant women. The MDRD equation is inaccurate for patients on drugs and with conditions that interfere with creatinine secretion (for example, cimetidine or trimethoprim) or creatinine assay (for example, diabetic ketoacidosis). In these cases, a 24-hour creatinine clearance may be necessary to accurately estimate kidney function.

NKF KDOQI STAGING[7] :

TABLE 1

Classification of Chronic Kidney Disease (CKD)	
Stage	**eGFR**
0	>90[a]
1	>=90[b]
2	60–89
3	30–59
4	15–29
5	<15

[a] With risk factors for ckd. [b] With demonstrated kidney damage (e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies.

The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m^2) attained during the third decade of life is ~1 mL/min per year per 1.73 m^2, reaching a mean value of 70 mL/min per 1.73 m^2 at age 70. The mean GFR is lower in women than

in men. For example, a woman in her 80s with a normal serum creatinine may have a GFR of just 50 mL/min per 1.73 m^2. Thus, even a mild elevation in serum creatinine concentration [for ex (1.5 mg/dL)], often signifies a substantial reduction in GFR in most individuals. Persistence in the urine of >17 mg of albumin per gram of creatinine in adult males and >25 mg albumin per gram of creatinine in adult females usually signifies chronic renal damage.

End-stage renal disease represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation. ESRD corresponds to stage 5CKD.

Cardiovascular Aspects of Chronic Kidney Disease :

BACKGROUND :

Cardiovascular disease is the main cause of death for patients with CKD. A study conducted by Foley[8] and colleagues, found that CKD was associated with a substantially increased incidence of congestive heart failure and of atherosclerotic vascular disease events, in both diabetics and nondiabetics**.**

Most clinical consequences of cardiac disease result from cardiomyopathy or ischemic heart disease. Cardiomyopathy may present as an enlarged, dilated left ventricle (LV) with or without systolic dysfunction, or as a hypertrophic ventricle with normal left ventricular volume and diastolic dysfunction.[9] Myocardial ischemia may also be present. Although symptoms of ischemic heart disease are most often attributable to the presence of critical coronary artery disease (defined as the presence of critical narrowing of the large coronary vessels due to atherosclerotic plaques), they may also result from non-atherosclerotic disease, associated with small vessel disease and LV hypertrophy. Myocardial infarction and angina can result from decreased perfusion of the myocardium from either cause. The

structure of large arteries can be altered not only by atherogenesis, but also by arteriosclerosis.[10]

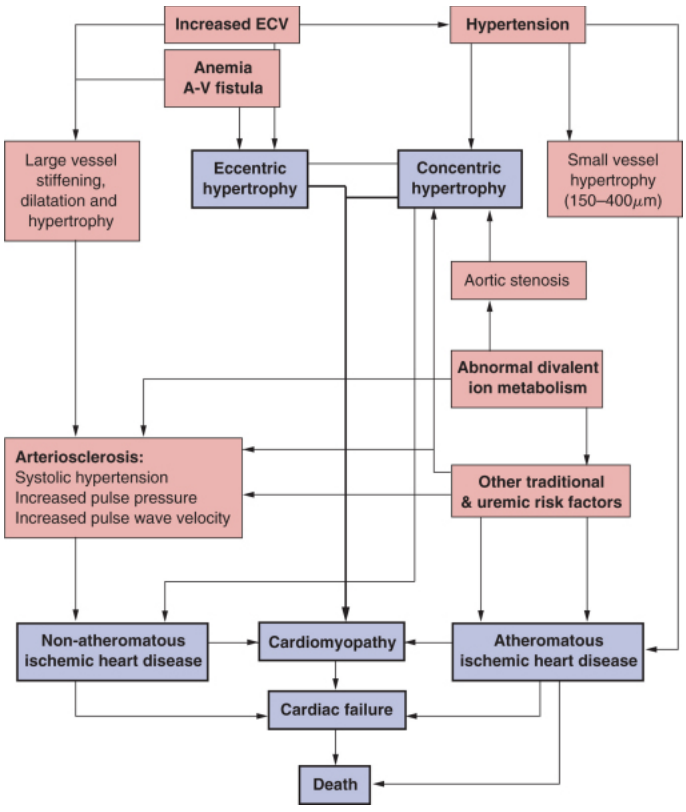
Intramural vascular remodelling occurs as a consequence of sustained hemodynamic overload causing conduit vessel dilatation and hypertrophy. The consequent increase in vessel stiffness and decreased compliance has been shown to contribute adversely to LV structure and function, and are strongly associated with an increased risk of mortality.[11]

Ischemic symptoms result from coronary artery disease or non-atherosclerotic ischemic disease. Arteriosclerosis contributes directly to ischemic symptoms, LV hypertrophy, and systolic dysfunction by increasing cardiac workload. Coronary artery disease predisposes to diastolic dysfunction and to systolic failure. Left ventricular hypertrophy is nearly always present in dilated cardiomyopathy, but also causes diastolic dysfunction with or without normal systolic function.

Cardiac disease can also result from the development of valvular heart disease. Most valvular lesions observed in patients with CKD are acquired and develop from dystrophic calcifications of the

valvular annulus and leaflets, particularly the aortic and mitral valves. Such calcification is now known to be present with a prevalence of up to 55% and 39% for the aortic and mitral valves respectively.[12,13] Aortic valve sclerosis is now also associated with an increased cardiovascular mortality in the general community.[14]

FIGURE 1 : CAUSES OF CARDIAC DEATH IN PATIENTS WITH CKD

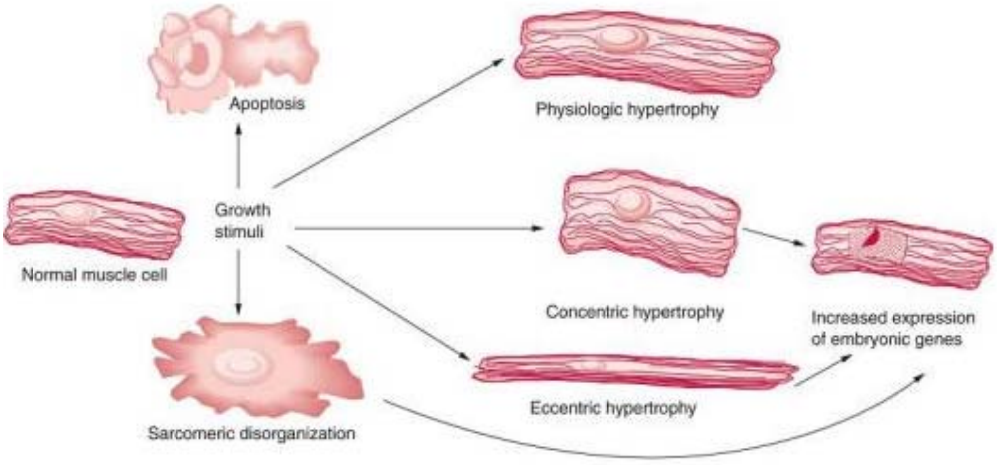


LEFT VENTRICULAR HYPERTROPHY:

Presentation of cardiovascular disease is influenced by the duration, severity, and type of renal disease. Left ventricular hypertrophy is already evident in 40% of patients with moderate renal insufficiency[15] and as high as 75% of those with ESRD.[16] Both forms (concentric and eccentric) are associated with an increased mortality risk in dialysis patients and associated risk factors, including hypertension, diabetes, tobacco use, and anemia predispose to the much more rapid development of symptomatic cardiomyopathy.[17] Such patients display a higher incidence of cardiovascular abnormalities at an earlier stage of CKD and a younger age, often becoming symptomatic or exhibiting significant morbidity well before reaching end-stage kidney function.

The characteristic changes in LV geometry subsequently are a progressive increase over time in both LV volume and LV mass, particularly during the first years,[17] and possibly more so in patients on peritoneal dialysis. [18] [19] As a result the geometry of the heart changes from concentric LV hypertrophy with normal LV volume to eccentric LV hypertrophy with dilatation, the end stage of this resulting in severe LV dilatation with systolic dysfunction.

FIGURE 2 : Morphology of ventricular myocytes in cardiac hypertrophy and failure



Concentric left ventricular hypertrophy (LVH) occurs in response to LV pressure overload, and eccentric LV hypertrophy in response to LV volume overload.

According to the law of Laplace, left ventricular tensile wall stress (s) relates directly to the intraventricular pressure (P) generated, as well as the internal radius (r) of the ventricular cavity. It is inversely proportional to the ventricular wall thickness (q) so that

$$s = Pr/2q.$$

Thus, the wall tension at any given pressure increases with the radius, and vice versa. The initial effects of LV hypertrophy are beneficial.

The energy-sparing effects of a stable parietal tensile stress permits the generation of higher intraventricular pressures without a large increase in wall stress. An appropriate relationship is maintained between the r/q ratio and systolic pressure generated, so that the intrinsic performance of the myocardium is not altered. Initially, hypertrophic responses to chronic pressure and/or volume overload are also adaptive. Modifications in the heart structure result in an increased work capacity while keeping the parietal tensile stress stable, thus sparing energy.[20]

Eventually however LV hypertrophy becomes maladaptive with a sustained imbalance between energy expenditure and production, resulting in a chronic energy deficit and myocyte death. [21,22] Consequences of these alterations are electrophysiological abnormalities and maintenance of systolic efficiency at the expense of impaired diastolic filling. Eventually, in conditions of chronic and sustained overload, the deleterious effects of hypertrophy, increased LV chamber pressure and fibrosis dominate, leading to the development of cardiomyopathy and LV failure.[22]

Interstitial myocardial fibrosis is a prominent finding in CKD[23]. The extent of myocardial fibrosis in dialysis patients is more marked

than in patients with diabetes mellitus or essential hypertension with similar LV mass.[24]

This is seen particularly in LV hypertrophy, more so in pressure than in volume overload, and is exacerbated by many factors, including male gender, senescence, ischemia, and effects of hormones such as catecholamines, angiotensin II, aldosterone, and transforming growth factors.[25]

LV functional disturbances :

Diastolic dysfunction:

CKD patients with LV hypertrophy often have some impairment in diastolic function. The degree of disturbance is probably more than that observed in those with hypertensive heart disease,[57] but milder than that observed in those with hypertrophic cardiomyopathy.[23,26,27] The abnormal ventricular filling in uremia results from increased LV stiffness caused by intramyocardial fibrosis and associated delayed relaxation. By virtue of an increase in LV stiffness, small changes in volume result in large changes in LV pressure, thus predisposing to symptomatic pulmonary edema.[28]

Systolic dysfunction :

Decreased systolic function may be observed in pre dialysis patients with cardiac disease or in patients with prolonged and marked hemodynamic overload. Approximately 15% of patients have systolic dysfunction by the time they reach stage 5.[15]

Renal transplantation has been shown to normalize systolic function in CKD patients with systolic dysfunction and subsequently to reduce but not normalize LV mass index,[29,30] although such improvement has not yet been shown to confer a survival benefit.[31]

Coronary artery disease:

Characterized by critical stenoses of the major coronary arteries, is highly prevalent in the CKD population, irrespective of underlying disease state such as diabetes and hypertension. Recently, two factors have received particular attention for their contribution to the development of atheroma in CKD: inflammation and vascular wall calcification.

Inflammation in general, and C-reactive protein (CRP) specifically, may contribute directly to the pathogenesis of atherosclerosis and its complications in patients with CKD. CRP has

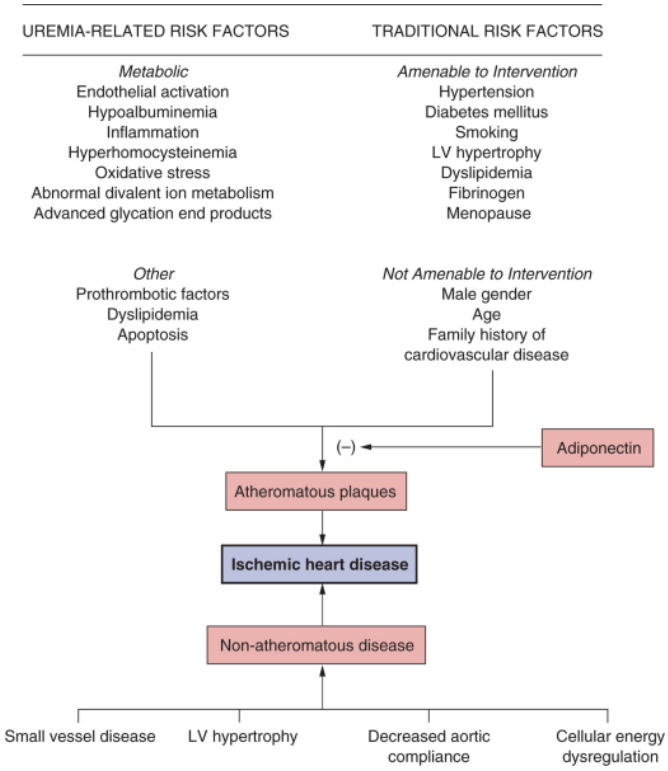
been shown to bind to damaged cells promoting activation of the complement system[32]; it displays calcium-dependent in vitro binding and aggregation of LDL and VLDL,[33] and is a potent stimulator of tissue factor by monocytes.[34]Epidemiological studies support its pathogenetic role as a cardiovascular risk factor in the general community, [35,36,37] which may be amenable to intervention by agents such as aspirin[36] and pravastatin.[38]

In CKD, the source of the (sometimes marked) elevation in CRP is uncertain. Potential sources include back filtration of endotoxin during dialysis,[39] type of vascular access type,[40] unrecognized infection, or bio-incompatibility of peritoneal dialysate.[41] C-reactive protein levels have been shown to have a powerful predictive capacity for mortality in both hemodialysis and peritoneal dialysis patients,[42] and to be an independent predictor of the number of atherosclerotic plaques and intima-media thickness in carotid arteries of hemodialysis[43] and predialysis patients,[44] respectively.

The deposition of calcium in vessel walls in patients with CKD has received greater attention nowadays. London and colleagues have recently examined the differences between intimal and medial aortic calcification.[45] Intimal calcification is associated with older age,

and a history or high risk of atherosclerosis, and medial calcification with younger age, lower risk of atherosclerosis, longer duration of hemodialysis, and serum calcium-phosphate abnormalities. Medial calcification implies arteriosclerosis with noncompliance of the large conduit vessels.

FIGURE 3: CAUSES OF ISCHEMIC HEART DISEASE IN CKD:



Valvular lesions :

Most valvular lesions observed in patients with CKD are acquired and develop from dystrophic calcification of the valvular annulus and leaflets, particularly the aortic and mitral valves.[46] Although most studies have identified abnormalities in calcium phosphate metabolism as the predominant underlying risk factor, additional factors include specific involvement of the posterior cusp, left atrial dilatation, duration of dialysis, and duration of pre-dialysis systolic hypertension. Factors associated with a decreased survival include severity of calcification, mitral regurgitation, and reduced left ventricular function.[47,48,49,50]

Pericardial Disease:

Pericardial pain with respiratory accentuation, accompanied by a friction rub, is diagnostic of uremic pericarditis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis can be accompanied by pericardial effusion that is seen on echocardiography and can rarely lead to tamponade. However, the pericardial effusion can be asymptomatic, and pericarditis can be seen without significant

effusion. Pericarditis is observed in advanced uremia, and with the advent of timely initiation of dialysis, is not as common as it once was.

RISK FACTORS FOR CARDIAC DYSFUNCTION IN CKD :

Effect of ageing :

In a study conducted by Ya Ting Lee and colleagues in 2008 [51] , they assessed the presence of Chronic Kidney Disease and subsequent changes of LV Geometry (LVG) over 4 Years in an apparently healthy population aged 60 and older. The prevalences of concentric remodelling, eccentric hypertrophy and concentric hypertrophy were significantly increased after 4 years. The LVG changes were only significant in subjects with CKD at baseline . If we stratified subjects into those with favorable (normal and concentric remodeling) and those with unfavorable LVG (eccentric hypertrophy and concentric hypertrophy), the presence of CKD was an independent predictor for unfavorable LVG after 4 years both in univariate and multivariate analysis.

Anemia :

Anemia in patients with CKD is a predominant manifestation, with high frequency but of moderate degree. The most likely cause is inadequate erythropoietin production[52]. Anaemia significantly worsens the cardiac function especially in patients on dialysis.[52] The morphologic feature of anemia consisted of: normochromic-normocytic (80%), hypochromic-microcytic (15%) and macrocytic anemia (5%)[53].

In a study conducted in Chennai , India[54], severity of anemia is found to have a significant correlation with LVH and secondary hyperparathyroidism in these patients.

CRP :

CRP is probably the most notorious inflammatory marker in CKD. It was first described in the 1930s for its role in serologic reactions to pneumococcal pneumonia. Interpretations of serum CRP levels and atherosclerotic cardiovascular disease[61]

Serum CRP Levels (mg/L)	Interpretation
<1	Normal
1 to 3	Possibly increased Cardiovascular risk
3 to 10	Highly likely increased Cardiovascular risk, common in stage 3 CKD
10 to 50	Common in stage 4 & 5 CKD
>50	Acute infection/inflammation Usually temporary.

Dyslipidemia :

The pattern of lipid profile did not change with severity of disease [62] and dyslipidaemia in patients were more in triglycerides, 68.3% and HDL, 63.5% than in TC, 22.2% and LDL, 17.5%. Dyslipidaemia does not only accelerate atherosclerosis in these patients but also progresses the renal disease. It is important to screen all patients with CKD for dyslipidaemias and treat them appropriately as they are considered “a very highrisk” group for cardiovascular disease. The target LDL should be maintained below 100 mg/ dl and target non HDL below 130 mg / dl[63].

Hypoalbuminemia :

Hypoalbuminemia is associated with LV dilatation and predisposes to both de novo cardiac failure and ischemic heart disease.[64] It is more characteristic of peritoneal dialysis than of hemodialysis patients, and in patients treated with each modality disease may result from different mechanisms. It is in fact likely that the path to death is different in hemodialysis patients, as a higher proportion develops cardiac failure, which predisposes to earlier death. In renal transplant recipients, hypoalbuminemia is an independent risk factor for the development of both de novo cardiac failure and ischemic heart disease, a similar observation to that made in dialysis patients. [65]

Hypertension :

It is probably the most common predictor of cardiovascular morbidity. Uncontrolled hypertension is by itself a significant risk factor for patients with CKD. Hypertension correlates well with LV mass (LVM). This has been proved in several studies.[65,67,68] Hypertension usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. Many studies have shown a relationship between the level of blood pressure

and the rate of progression of both diabetic and non-diabetic kidney disease. Left ventricular hypertrophy and dilated cardiomyopathy are among the strongest risk factors for cardiovascular morbidity and mortality in patients with CKD and are thought to be related primarily, but not exclusively, to prolonged hypertension and ECFV overload.

The absence of hypertension may signify the presence of a salt-wasting form of renal disease, the effect of antihypertensive therapy, or volume depletion or may signify poor left ventricular function. Chronic ECFV overload is also a contributor to hypertension, and improvement in blood pressure can often be seen with the use of oral sodium restriction, diuretics, and fluid removal with dialysis. However , because of activation of the renin-angiotensin-aldosterone axis and other disturbances in the balance of vasoconstrictors and vasodilators, some patients remain hypertensive despite ECFV status.

AIMS AND OBJECTIVES

1. To assess the cardiac status in non diabetic, non smoker chronic kidney disease patients in our hospital.
2. To screen these patients for cardiac risk factors
3. To compare the different methods of estimating LV mass including LV mass obtained by conventional echocardiography, LV mass adjusted to body surface area and LV mass adjusted to height and correlate the LV mass in CKD patients and controls.
4. To assess the effect of uncontrolled hypertension on LV mass in these individuals.
5. To assess diastolic and systolic dysfunction in these individuals.
6. To evaluate the usefulness of Tissue Doppler imaging (TDI) over conventional echocardiography for cardiac assessment in CKD patients.
7. To correlate LV mass with the severity of CKD.

MATERIALS AND METHODS

Setting : Department of Medicine,
Government Rajaji Hospital.

Design : Descriptive study.

Period of study : July 2010 to December 2010.

Ethical approval : Obtained from ethical committee headed by The Dean, Government Rajaji Hospital, Madurai.

Consent : Informed consent obtained from all patients

Statistical software : SPSS Version 17.0

Study population: OP and IP patients in Medicine and Nephrology Departments.

Cases :

Inclusion criteria :

(1). All cases of non diabetic and non smoker chronic kidney disease.

Exclusion criteria :

1. Patients with H/o coronary artery disease, valvular heart disease or any form of congenital heart disease.
2. Patients with H/o diabetes.
3. Patients with H/o smoking.
4. Patients with evidence of diabetic retinopathy.
5. Patients with active or recent infection over the past 3 weeks.
6. Patients on hemodialysis.
7. Patients with A-V fistulas.
8. Patients on erythropoietin treatment.
9. Patients with poor echo window.
10. Patients not giving consent.

65 CKD patients were taken as cases and 20 healthy volunteers were taken as controls. Informed consent was obtained from all the patients. A meticulous history was taken regarding the duration of CKD, duration of hypertension, family history of diabetes, hypertension and CKD. The presence of complaints suggestive of volume overload and uraemic symptoms were carefully elicited.

The fundus was carefully examined for the presence of any evidence of diabetic retinopathy and those cases were excluded from

the study. Meticulous blood pressure recording including 3 recordings in sitting posture in left upper arm and the mean value of the three was taken as blood pressure. Pulse pressure is calculated as the difference between systolic and diastolic blood pressure.

The height and weight of the patient were measured and the body surface area is calculated using the formula of DuBois and DuBois:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

where the weight is in kilograms and the height is in centimeters.

All patients underwent the following blood investigations including blood sugar, urea, serum creatinine, ESR, CRP, Hb%, TGL. Patients whose random blood sugar was more than 140 were further evaluated with fasting and post prandial blood sugar and if found to be abnormal were eliminated from the study.

eGFR was calculated from serum creatinine values using 1. Cockroft Gault equation :

$$\text{Creatinine clearance} = \frac{(140\text{-age}) \times \text{bodyweight (kg)}}{72 \times \text{S.Creat (mg/dl)}} \times 0.85 \text{ (for women)}$$

and also using 2. MDRD formula

Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

Multiply by 0.742 for women, Multiply by 1.21 for African Americans.

NKF-KDOQI staging of CKD was applied using MDRD formula and stage of CKD is determined. Electrocardiography(ECG) was done in all patients to look for evidence of LVH, electrolyte disturbances, and coronary artery disease

Echocardiography :

Basic principles :

It is a simple, non invasive investigation widely available which gives accurate measurement of cardiac function and anatomy of heart. It uses ultrasound to study the disposition and movement of valves and other structures within the heart. It depends on the reflection of ultrasound waves at interfaces between blood and more solid tissues.

In M mode echocardiography, the ultrasound waves are focussed into a narrow beam and the output is a graph against time of the movement, relative to the chest wall of those structures through which

the beam passes. Accurate measurements can be made of cardiac dimensions.

In 2 D echocardiography, the ultrasound beam was swung back and front over an arc or sector and the resulting information is synthesised into a two dimensional map or picture of the position of the reflecting structures on a screen. The picture is the equivalent of a slice through the heart.

In real time echocardiography, the beam oscillates very rapidly and the ultrasound image accurately produces the movement of structures in the living heart. This is useful for assessing intracardiac mass and vegetations.

Doppler echocardiography depends on the fact that sound waves reflected from moving objects such as intracardiac red blood cells(RBC's) undergo a frequency shift. This can be used to detect the direction and speed of movement of RBC's and thus of the blood in heart.

Continuous wave Doppler uses a narrow beam of ultrasound in a way analogous to M mode echocardiography.

Pulsed wave Doppler can sample movement of blood at different depths beneath the transducer and is frequently combined with 2 D echocardiography as to examine blood flow in relation to cardiac anatomy. Gradients of flow across valves can be calculated using Doppler. Cardiac output can also be measured.

Tissue Doppler imaging has the advantage of more accuracy in assessing diastolic and systolic dysfunction than conventional echocardiography.

All patients in the study (both cases and controls) underwent echocardiography both 2D and TDI using PHILIPS IE 33 ECHOCARDIOGRAPHY machine and cardiac function is assessed.

Echocardiographic parameters assessed:

Left Ventricular Mass Measurement :

Left ventricular mass is generally calculated as the difference between the epicardium delimited volume and the left ventricular chamber volume multiplied by an estimate of myocardial density. Following this principle, several methodologies have been used to calculate left ventricular mass.

Both M-mode and two-dimensional imaging can be employed to calculate left ventricular mass. M-mode imaging allows better endocardial border definition as it has greater resolution due to higher frame-rate, as long as adequate ultrasound beam positioning is ensured and ventricle shape approaches normality. Two-dimensional imaging, on the other hand, depicts the "real" ventricular shape and identifies regional motion abnormalities. However, the quality of two-dimensional imaging may be limited due to both lower lateral resolution and frame-rate. Two-dimensional images are usually acquired both in parasternal and apical views, depending on the geometrical formulas that are used.

Devereux and colleagues proposed a new adjusted equation, using the ASE convention and it is so far widely accepted.

LV mass (ASE): 0.8 (1.04 ([LVIDD + PWTD + IVSTD]3-[LVIDD]3))+ 0.6 g.

The body surface area correction, using the Dubois formula , reduces variability due to body size and gender , but this index underestimates LV mass in the upper range of the body surface area distribution. Adjustment of LV mass with body surface area would

imply that obese patients are expected to have higher LV mass estimations per se.

In this scenario, height-based adjustments can more accurately estimate LV mass and the resulting cardiovascular risk associated with LVH in the obese. Height to the power 2.7, derived from regression models in normal samples from De Simone and co-workers, appears to offer the most accurate estimation of LV hypertrophy and risk factors for pathologic changes in the heart structure, particularly in obese subjects.

Zoccali and colleagues found LVH indexed by height$^{2.7}$ to be a better predictor of cardiovascular events than LVH indexed using body surface area.

Liao and colleagues studied 988 patients and identified progressive increments in death rates with both body surface area and with height$^{2.7}$ indexing criteria. Subjects simultaneously classified as LVH with body surface area and height$^{2.7}$ criteria had increased average LV mass and a 3-fold increase in death rates, while those classified as LVH only when indexed by bsa had no increase in future cardiovascular events.

In our study LV mass is determined by M mode echocardiography and is adjusted to body surface area and also to height to the power of 2.7.

The cut off values for LVH are as adopted from American College of Echocardiography guidelines.

LV mass :

Normal LV mass in males is < 201 grams and in females, < 151.

Mild LVH in males is 201 to 227 grams and in females 151 to 171.

Moderate LVH in males is 228 to 254 and in females 172 to 192.

Severe LVH in males is ≥ 255 and in females ≥ 193.

LVMI (LV mass adjusted to body surface area) :

Normal LVMI in males is < 103 g/m^2 and in females, < 89 g/m^2.

Mild LVH in males is 103 to 116 g/m^2 and in females 89 to 100 g/m^2.

Moderate LVH in males is 117 to 131 g/m^2 and in females 101 to 112 g/m^2.

Severe LVH in males is ≥ 131 g/m^2 and in females ≥ 113 g/m^2.

LV mass adjusted to $height^{2.7}$:

Normal LV mass is <49.2 g and in females <46.7.

Mild LVH is 49.2 to 60 and in females 46.7 to 55.

Moderate LVH in males is 60 to 80 and in females 55 to 65.

Severe LVH in males is > 80 and in females >66.

This is in accordance with American College of Cardiology and American Society of Echocardiography guidelines.

LV Ejection Fraction measurement (LVEF) :

LVEF as determined by LV volumes in apical 2 chamber view. LV volumes were measured by area – length method both in end diastole (LVVd) and end systole (LVVs).

LVEF = (LVVd – LVVs) / LVVd.

The mean LVEF as per recent ASE guidelines were 63.8± 5. In our study, cases having less than 55 % are taken as having systolic dysfunction.

E/A ratio :

Diastolic dysfunction was determined by 2 D echocardiography by determining ratio of peak early diastole velocity (E) divided by peak atrial filling velocity of LV(A). Normal value of E was

0.61 m/ ± 0.14 and A was 0.48 m/ sec ± 0.14 with a normal E/A ratio of 1.40±0.54.

Diastolic dysfunction was considered when E/A ratio was found to be less than 1.

But the fallacy in 2 D Doppler is there is pseudo normalisation in cases of grade 2 diastolic dysfunction. This can be overcome by using Tissue Doppler imaging where value measured is E'/A' and there will not be any pseudo normalisation.

There are four basic Echocardiographic patterns of diastolic heart failure, graded I to IV.

1. The mildest form is called an abnormal relaxation pattern or grade I diastolic dysfunction. On the mitral inflow Doppler echocardiogram, there is reversal of the normal E/A ratio. Many grade I patients will not have any clinical signs or symptoms of heart failure.

2. Grade II diastolic dysfunction is called pseudonormal filling dynamics. This is considered moderate diastolic dysfunction and is associated with elevated left atrial filling pressures. These patients more commonly have symptoms of heart failure.

3. Grade III diastolic dysfunction patients will demonstrate reversal of their diastolic abnormalities on echocardiogram when they perform the Valsalva maneuver and are called reversible restrictive diastolic dysfunction.
4. Grade IV diastolic dysfunction patients will not demonstrate reversibility of their echocardiogram abnormalities and are therefore called fixed restrictive diastolic dysfunction.

In our study diastolic function is assessed using both E/A and E'/A'. And the results of both these recordings compared.

In our study, systolic BP between uncontrolled and controlled individuals were compared with LV mass obtained using 2 D echo and adjusted for body surface area and height. BP was assumed as controlled if SBP was less than 140 with or without anti hypertensives.

In our study, the incidence of anaemia, increased triglyceride and CRP positivity in between CKD patients and controls were compared.

Computer analysis of statistical data were obtained using SPSS version 17.0 and the results were analysed.

RESULTS AND ANALYSIS

Stage of CKD and LVM :

Table -1

			LVM				
			Normal	Mild	Moderate	Severe	Total
Category	Control	Count	13	5	1	1	20
		Percent	65.0%	25.0%	5.0%	5.0%	100.0%
	Stages 2,3	Count	8	3	2	2	15
		Percent	53.3%	20.0%	13.3%	13.3%	100.0%
	Stages 4,5	Count	19	8	4	19	50
		Percent	38.0%	16.0%	8.0%	38.0%	100.0%
	Total	Count	40	16	7	22	85
		Percent	47.1%	18.8%	8.2%	25.9%	100.0%

LV mass increases directly in proportion to the severity of CKD. 65 % of controls are having normal LV mass. 5% (1 control) of controls had severe LVH. Whereas, in patients with stage 2 and 3 CKD, it was 13.3% (2 patients) and in stage 4 and 5 CKD, it was 38% (19 patients)

Stage of CKD and LVMI (bsa) :

Table -2

			LVMIbsa				
			Normal	Mild	Moderate	Severe	Total
Category	Stages 2,3	Count	9	3	2	1	15
		Percent	60.0%	20.0%	13.3%	6.7%	100.0%
	Stages 4,5	Count	21	12	10	7	50
		Percent	42.0%	24.0%	20.0%	14.0%	100.0%
	Total	Count	30	15	12	8	65
		Percent	46.2%	23.1%	18.5%	12.3%	100.0%

LVMI (LVM adjusted to body surface area) varies directly in relation to increasing severity of CKD. In patients with stage 2 and 3 CKD, 13.3% had moderate LVH and 6.7% had severe LVH. Whereas in patients with stage 4 and 5 CKD, it increase to 20% and 14% respectively.

Stage of CKD and LVMHt :

Table -3

			LVMht				
			Normal	Mild	Moderate	Severe	Total
Category	Control	Count	15	3	1	1	20
		Percent	75.0%	15.0%	5.0%	5.0%	100.0%
	Stages 2,3	Count	9	2	3	1	15
		Percent	60.0%	13.3%	20.0%	6.7%	100.0%
	Stages 4,5	Count	13	13	9	15	50
		Percent	26.0%	26.0%	18.0%	30.0%	100.0%
	Total	Count	37	18	13	17	85
		Percent	43.5%	21.2%	15.3%	20.0%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	18.286	6	.006

A significant correlation exists between stage of CKD and LV mass adjusted to height (p value of 0.06) . 75 % of controls are having normal LV mass whereas 48 % of patients with stages 4 and 5 CKD are having moderate to severe LVH.

Systolic BP and LV mass :

Table -4

			LVM				
			Normal	Mild	Moderate	Severe	Total
sysBP	Controlled	Count	29	11	1	9	50
		Percent	58.0%	22.0%	2.0%	18.0%	100.0%
	Uncontrolled	Count	11	5	6	13	35
		Percent	31.4%	14.3%	17.1%	37.1%	100.0%
Total		Count	40	16	7	22	85
		Percent	47.1%	18.8%	8.2%	25.9%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.387[a]	3	.006

A significant correlation exists between systolic BP and LV mass with a p value of 0.006. 54.2% of patients with uncontrolled BP have evidence of moderate to severe LVH. Whereas it is 20 % in those with controlled BP.

Systolic BP and LVMI (bsa) :

Table -5

			LVMIbsa				
			Normal	Mild	Moderate	Severe	Total
sysBP	Controlled	Count	34	8	4	4	50
		Percent	68.0%	16.0%	8.0%	8.0%	100.0%
	Uncontrolled	Count	12	11	8	4	35
		Percent	34.3%	31.4%	22.9%	11.4%	100.0%
Total		Count	46	19	12	8	85
		Percent	54.1%	22.4%	14.1%	9.4%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	9.993[a]	3	.019

A significant correlation exists between systolic BP and LV mass index adjusted to body surface area with a p value of 0.019. 34.3% of patients with uncontrolled BP have evidence of moderate to severe LVH. Whereas it is 16 % in those with controlled BP.

Systolic BP and LVM ($ht^{2.7}$)

Table -6

			LVM /$ht^{2.7}$				
			Normal	Mild	Moderate	Severe	Total
sysBP	Controlled	Count	29	10	4	7	50
		Percent	58.0%	20.0%	8.0%	14.0%	100.0%
	Uncontrolled	Count	8	8	9	10	35
		Percent	22.9%	22.9%	25.7%	28.6%	100.0%
Total		Count	37	18	13	17	85
		Percent	43.5%	21.2%	15.3%	20.0%	100.0%

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.331[a]	3	.006

A significant correlation exists between systolic BP and LV mass adjusted to height with a p value of 0.006. 54.3% of patients with uncontrolled BP have evidence of moderate to severe LVH. Whereas it is 22 % in those with controlled BP.

Stage of CKD and E/A

Table -7

			EA		
			< 1	>=1	Total
Category	Control	Count	1	19	20
		Percent	5.0%	95.0%	100.0%
	Stages 2,3	Count	4	11	15
		Percent	26.7%	73.3%	100.0%
	Stages 4,5	Count	25	25	50
		Percent	50.0%	50.0%	100.0%
	Total	Count	30	55	85
		Percent	35.3%	64.7%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	13.261[a]	2	.001

A significant correlation exists between stage of CKD and E/A ratio with a p value of 0.001. 5% of controls were having an E/A ratio of less than 1. Whereas it was 25.3 % in patients in patients with stage 2 and 3 CKD and 50% in patients with stage 4 and 5 CKD

Stage of CKD and E'/A' :

Table - 8

			E'/A'1		
			< 1	>=1	Total
Category	Control	Count	1	19	20
		Percent	5.0%	95.0%	100.0%
	Stages 2,3	Count	4	11	15
		Percent	26.7%	73.3%	100.0%
	Stages 4,5	Count	41	9	50
		Percent	82.0%	18.0%	100.0%
	Total	Count	46	39	85
		Percent	54.1%	45.9%	100.0%

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	39.639[a]	2	.000

A highly significant correlation with a p value of 0.000 was obtained between stage of CKD and E'/A'. 5% of controls were having an E/A ratio of less than 1. Whereas it was 26.7 % in patients in patients with stage 2 and 3 CKD and 82% in patients with stage 4 and 5 CKD.

Tissue Doppler imaging using E'/A' detects more number (82%) of diastolic dysfunction when compared to conventional echo (E/A) which detects only 50% .

Stage of CKD and EF :

Table -9

			EF		
			<= 55	>55	Total
Category	Control	Count	0	20	20
		Percent	.0%	100.0%	100.0%
	Stages 2,3	Count	1	14	15
		Percent	6.7%	93.3%	100.0%
	Stages 4,5	Count	25	25	50
		Percent	50.0%	50.0%	100.0%
	Total	Count	26	59	85
		Percent	30.6%	69.4%	100.0%

Ejection fraction decreases in direct proportion to severity of CKD. In controls, there are no individuals with EF <55 whereas it is 6.7% in stages 2 and 3 CKD and it is 50 % in patients with stages 4 and 5 CKD. EF is one of the markers to assess the severity of renal failure.

DISCUSSION

Cardio vascular disease is the major cause of mortality in patients with CKD. Indian CKD patients are more prone to cardiovascular disease than in the West due to ethnic, socio economic and other cardiovascular risk factors. They tend to develop CKD at least 2 decades earlier than their western counterparts and many fail to reach the hospital in an earlier stage due to lack of awareness and socio economic factors. The burden of CKD is increasing worldwide and it has doubled over the past 15 yrs. CKD in Indian scenario is a burden to the society and family.

Assessment of cardiac function in CKD should be started as soon as CKD is diagnosed and should be done periodically to assess the prognosis in these patients and early initiation of treatment is recommended to halt the progression of disease. LV hypertrophy is an independent predictor of mortality in patients with CKD. Emergence of grade 3 and 4 diastolic dysfunction and systolic dysfunction has been associated with a grave prognosis in patients with CKD.

We analysed 65 CKD patients and 20 controls from the Department of Medicine and Department of Nephrology from Government Rajaji Hospital. Out of CKD patients, males constitute

about 57% (number of patients 37) and females were 43% (number of patients 28). Among the controls, 2(60%) were males and 8(40%) females.

Age:

The minimum age in control group was 28 and the maximum age 61 with mean age of 43.35. In CKD group, minimum age was 28 and maximum age was 66. Mean age of CKD patients analysed was 43.43. The CKD patients in our study and controls were comparable in age and sex.

As per Indian study published by Dr.S.Agarwal from New Delhi in 2003, the mean age of Indian CKD was found to be 35-45 yrs. Mean age of western CKD population was 51-60 yrs. Our study correlates well with the findings of Indian literature. It is probably attributed to increased prevalence of streptococcal infections in Indian scenario whereas in western countries diabetes and hypertension in old age are responsible for majority of CKD. As per our study, CKD is a problem in middle age group.

Anaemia :

The Hb level in controls varied from 8 to 14gm with a mean of 11.02gm. In stages 4 & 5 CKD the Hb levels varied from 4 to 12gm with a mean 8.46gm. In 2005 Suega K. Bhakta[69] confirmed an increased prevalence of anaemia with worsening degrees of renal failure. The severity of anemia correlates with the severity of renal failure in our study.

Anaemia is one of the most important factors worsening cardiac status and correction of anemia with iron supplements and erythropoietin in CKD population is recommended to prevent cardiac mortality.

ESR :

Fernandes et al found ESR does not correlate with degree of anemia in CKD population. In our study ESR did not correlate with the severity of anemia. A raised ESR is a marker of low grade chronic inflammation in CKD, especially in hemodialyzed patients.[72]

CRP :

CRP was positive in 21% (14 patients) of CKD patients in our study. In none of the controls, it was positive. CRP carries a great

impact on cardiovascular mortality in CKD patients and the level of CRP correlates well with adverse cardiovascular outcome.

Triglyceride :

The mean triglyceride levels in stages 4 & 5 CKD is 200.04 whereas in controls it is 181.15. But no significant relation can be obtained between the two values. Triglycerides do increase with increasing stages of CKD compared to controls and early institution of treatment protects against both cardiovascular complications and further worsening of renal failure.

LV hypertrophy :

LV mass :

LV mass predicts mortality in general. We try to correlate LB mass to the severity of CKD. 5% of controls, (1 control) had severe LVH. In patients with stage 2 and 3 CKD, it was 13.3%. In stage 4 and 5 CKD, it was 38%. It correlates well with another study published in Indian journal of Nephrology in 2003 in which study the mean LV mass varies directly in relation to stage of CKD.

This is the graph showing LV mass relation to stage of CKD in the study from journal of nephrology[73]. It is comparable to Figure 3 in our study.

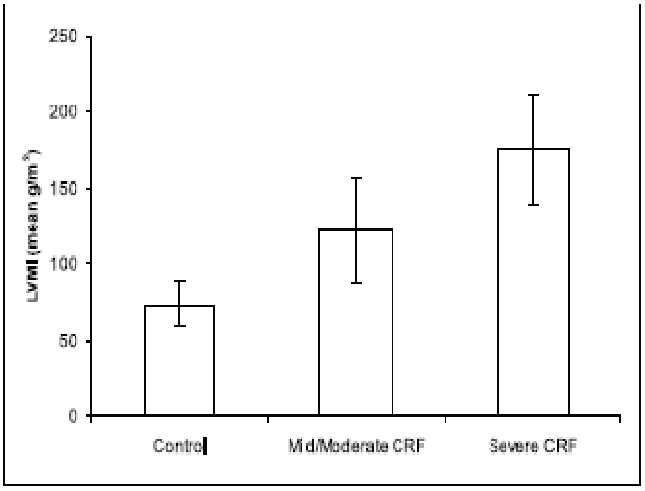


Figure 13

LV mass index (bsa) :

LVMI (LVM adjusted to body surface area) varies directly in relation to increasing severity of CKD. In patients with stage 2 and 3 CKD 13.3% had moderate LVH and 6.7% had severe LVH. Whereas in patients with stage 4 and 5 CKD, it increase to 20% and 14% respectively. But no significant relation could be obtained. This is in accordance with the study conducted in Nigeria[74], which concluded that the lowest prevalence of LVH was observed when LVM was

indexed to BSA. Indexation to BSA offsets the independent impact of obesity on LV mass which decrease sensitivity of LV mass index for measuring LV mass.

LV mass adjusted to height$^{2.7}$:

A significant correlation exists between stage of CKD and LV mass adjusted to height (p value of 0.06) . 75 % of controls are having normal LV mass whereas 48 % of patients with stages 4 and 5 CKD are having moderate to severe LVH.

This is in accordance with other studies including the report from the Strong Heart Study group showed that the presence of LVH identified by LV mass normalized for height to allometric powers is associated with higher incident cardiovascular events than is LVH detected by normalization for body surface area[75]. Another study[74] concludes that the highest prevalence of LVH was when LVM was indexed to the power of 2.7.

Systolic BP :

A significant correlation exists between systolic BP and LV mass with a p value of 0.006. 54.2% of patients with uncontrolled BP have evidence of moderate to severe LVH. Whereas it is 20 % in those

with controlled BP. This is in accordance with harrisons textbook of internal medicine 17th edition, which states that hypertension as the single most important predictor of LV mass.

Significant correlation is also obtained between uncontrolled systolic BP and LV mass index (0.019) and LV mass adjusted to height(0.006)

Management of systemic hypertension drastically improves the morbidity and mortality in CKD patients irrespective of cause. Target BP to be maintained less than 130/80 and 125/75 in those with proteinuria.

E / A ratio :

A significant correlation exists between stage of CKD and E/A ratio with a p value of 0.001. 5% of controls were having an E/A ratio of less than 1. Whereas it was 25.3 % in patients in patients with stage 2 and 3 CKD and 50% in patients with stage 4 and 5 CKD.

E'/A' ratio :

A highly significant correlation with a p value of 0.000 was obtained between stage of CKD and E'/A'. 5% of controls were having an E/A ratio of less than 1. Whereas it was 26.7 % in patients in

patients with stage 2 and 3 CKD and 82% in patients with stage 4 and 5 CKD.

Tissue Doppler imaging using E'/A' detects more number (82%) of diastolic dysfunction when compared to conventional echo(E/A) which detects only 50% . As there is pseudo normalisation of flow pattern, it is difficult to interpret whether a normal E/A ratio is associated with normal cardiac function or grade 2 diastolic dysfunction. This is overcome by Tissue Doppler imaging. This was supported by a study from Shirley Yumi Hayashi[76], from Sweden who compared tissue Doppler with conventional echocardiography in CKD patients and they concluded that in patients with advanced renal failure, TDI revealed more accentuated diastolic dysfunction associated with increased systolic blood pressure (SBP) and increased levels of PTH. TDI also demonstrated disturbances in contractility and contraction in patients with LVH, which could not be detected by conventional echocardiography.

LVEF:

Ejection fraction decreases in direct proportion to severity of CKD. In controls, there are no individuals with EF <55. Whereas it is

6.7% in stages 2 and 3 CKD and it is 50 % in patients with stages 4 and 5 CKD.

The prevalence of diastolic dysfunction is 82 % which is much more than systolic dysfunction of 50 %. It suggests that diastolic dysfunction was the first to appear in renal failure.

Mitral regurgitation occurred in 6 patients in our study. Aortic regurgitation in 3 and tricuspid regurgitation in 2 patients. pericardial effusion was observed in 4 patients in the study.

SUMMARY

Patients with chronic kidney disease (CKD) most often present with non specific complaints or often asymptomatic detected by routine biochemical investigations. A high degree of suspicion is needed to detect early stages of CKD. Any patient diagnosed as CKD irrespective of the stage should be completely evaluated for establishing the cause of CKD and also establish the various hemodynamic abnormalities associated with CKD.

In particular, importance should be given for evaluating the cardio vascular risk factors and cardiac function in CKD patients.

Co morbid conditions which worsen the cardiac status such as alcohol, smoking should be curtailed. In diabetics, meticulous control of blood sugar is mandatory taking care to avoid hypoglycaemia. Anaemia as shown in our study is an important co morbid condition increasing in severity with stage of CKD. All patients should be evaluated for the cause of anaemia and treated accordingly, if needed with erythropoietin.

Hypertension, especially if uncontrolled, as shown in our study correlates significantly with LV mass and in turn cardiac mortality.

Echocardiography is one of the best non invasive means of evaluating cardiac function in patients with CKD. LV mass, diastolic and systolic dysfunction correlates with stage of CKD.

The following points were noted in our study :

1. Anaemia increases in severity with stage of CKD. It further worsens the cardiac function irrespective of pre existing cardiac status.
2. Hypertension, especially if uncontrolled significantly correlates with LV mass with a p value of 0.006
3. LV mass increases directly in proportion to stage of CKD.
4. LV mass adjusted to body surface area called as LV mass index increases in direct proportion to stage of CKD but statistically significant relation could not be obtained.
5. LV mass adjusted to height to the power of 2.7 has significant correlation with stage of CKD.
6. LV mass index adjusted to height is the best predictor of LV mass in patients with CKD and correlates directly to cardiovascular mortality.
7. E/A ratio predicts the diastolic dysfunction which worsens progressively with increasing stages of CKD.

8. E'/A' measured by tissue Doppler imaging correlates with diastolic dysfunction which worsens with stage of CKD.
9. E'/A' is a better predictor of diastolic dysfunction than E/A as it avoids the fallacy of pseudo normalisation.
10. EF worsens with advancing kidney disease and predicts systolic dysfunction.
11. Other cardiac lesions infrequently noted include regurgitant lesions of mitral, tricuspid and aortic valves.
12. Pericardial effusion was noted in 4 patients in the study.
13. No case of aortic / mitral annular calcifications are noted in the study.

Echocardiography provides a valuable tool in CKD patients even if asymptomatic and should be regularly followed up.

Echocardiographic evaluation should be included as a routine investigation in CKD patients.

CONCLUSION

The burden of cardiovascular disease in patients with chronic kidney disease is high. Multiple traditional cardiac risk factors and uraemia related risk factors coexist.

Echocardiography should be performed early in the course of CKD. Tissue Doppler imaging should be performed in all cases for accurate assessment of cardiac status. In the cardiovascular system, LV hypertrophy, LV diastolic and systolic dysfunction predominate and worsens with stage of CKD. Strict control of BP is advocated. Anaemia should be promptly corrected. Treatment of dyslipidemia is warranted in those deserving treatment. CRP is an important risk factor and should be duly monitored and treated with aspirin and statins. Early institution of dialysis partially protects against these cardiac complications and improves cardiac function.

1) CKD is a burden in middle age group in our study.
2) Cardiac mortality is high in CKD patients.
3) Anemia correlates with cardiac function and correction of anemia decreases cardiac mortality.
4) Hypertension statistically correlates with LV mass.
5) Diastolic and systolic dysfunction worsens with stage of CKD.
6) Echocardiographic evaluation is a must in CKD population.

FIGURE – 3

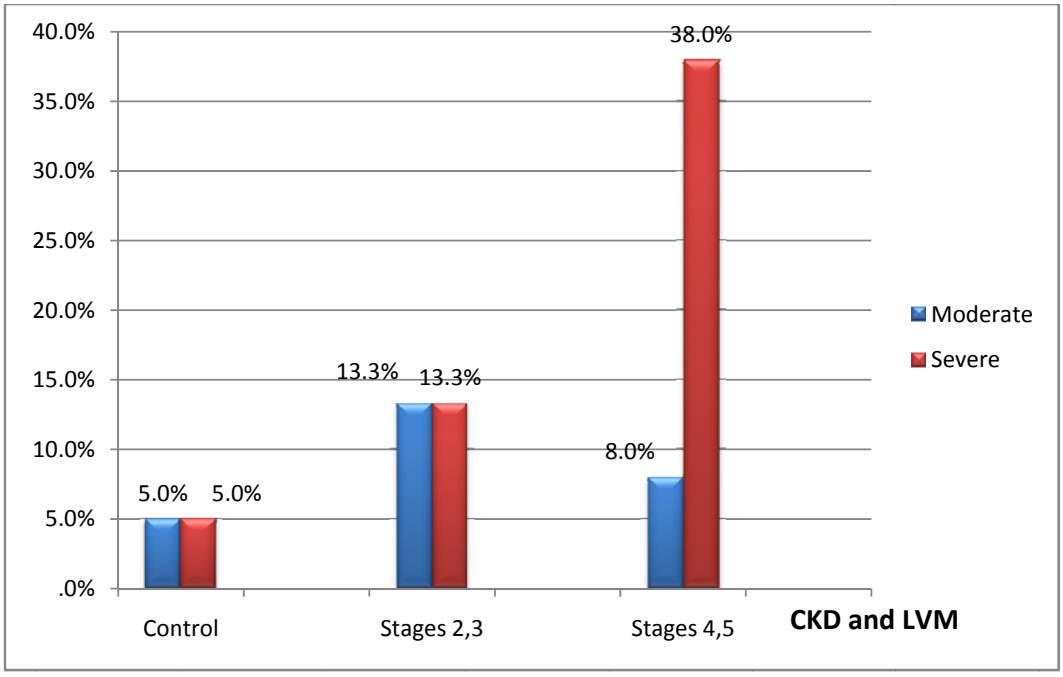

40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
.0%
5.0%
5.0%
13.3%
13.3%
8.0%
38.0%
Control
Stages 2,3
Stages 4,5
CKD and LVM
Moderate
Severe

FIGURE - 4

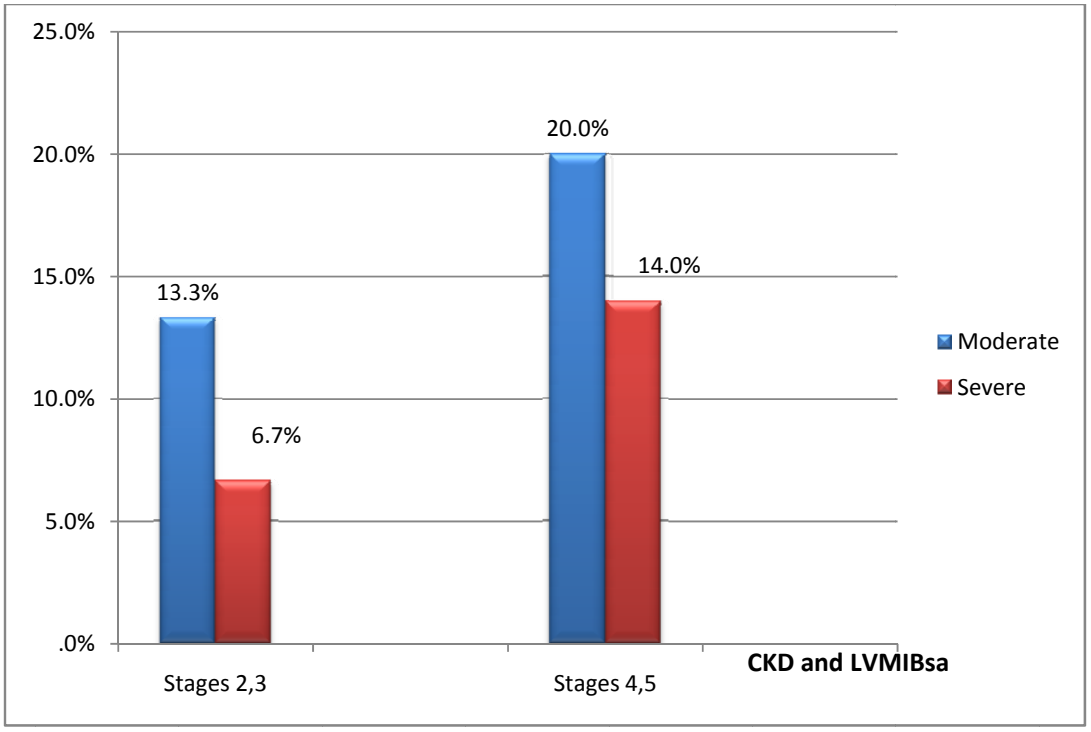

25.0%
20.0%
15.0%
10.0%
5.0%
.0%
13.3%
6.7%
20.0%
14.0%
Moderate
Severe
Stages 2,3
Stages 4,5
CKD and LVMIBsa

FIGURE - 5

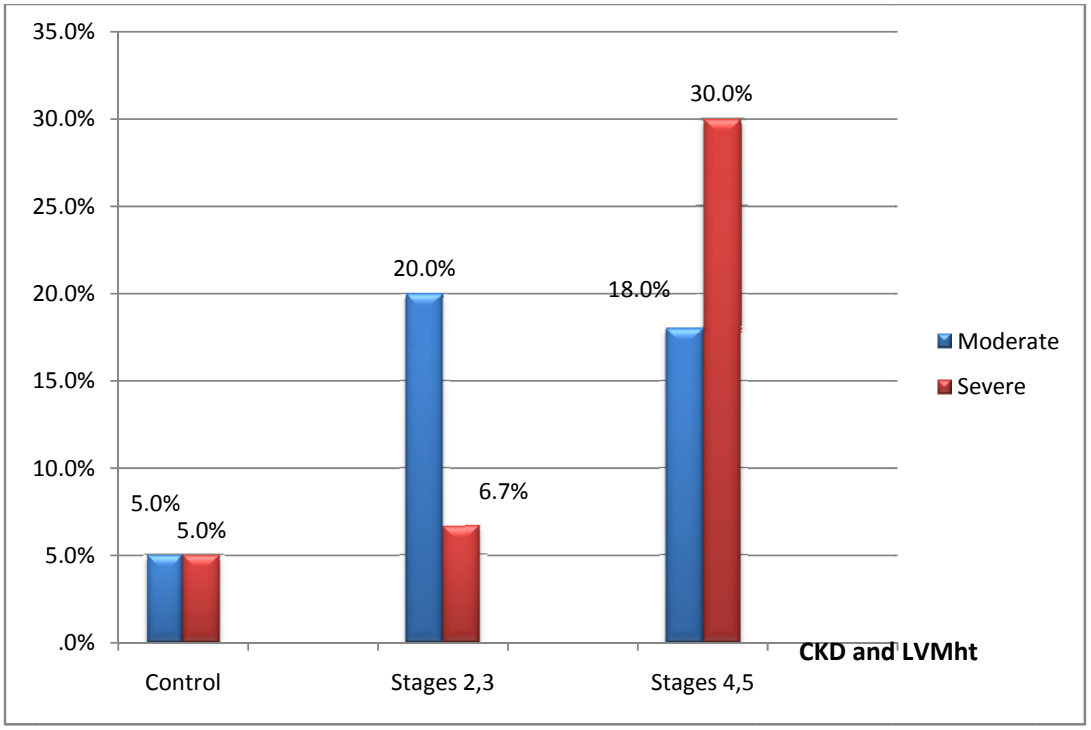

35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
.0%
5.0%
5.0%
20.0%
6.7%
18.0%
30.0%
Control
Stages 2,3
Stages 4,5
Moderate
Severe
CKD and LVMht

FIGURE - 6

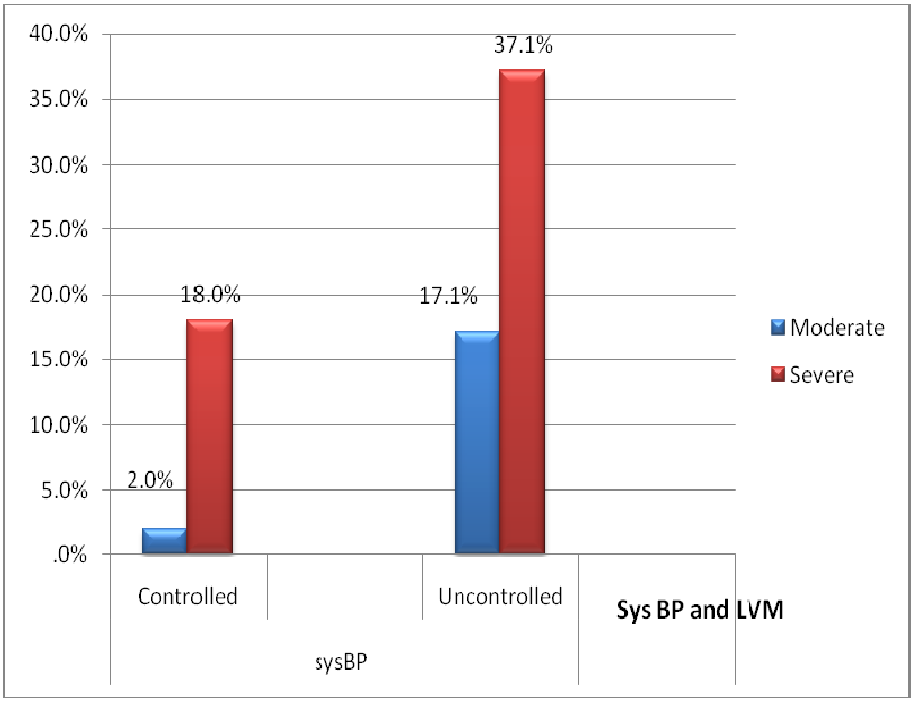

40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
.0%
2.0%
18.0%
17.1%
37.1%
Moderate
Severe
Controlled
Uncontrolled
sysBP
Sys BP and LVM

FIGURE - 7

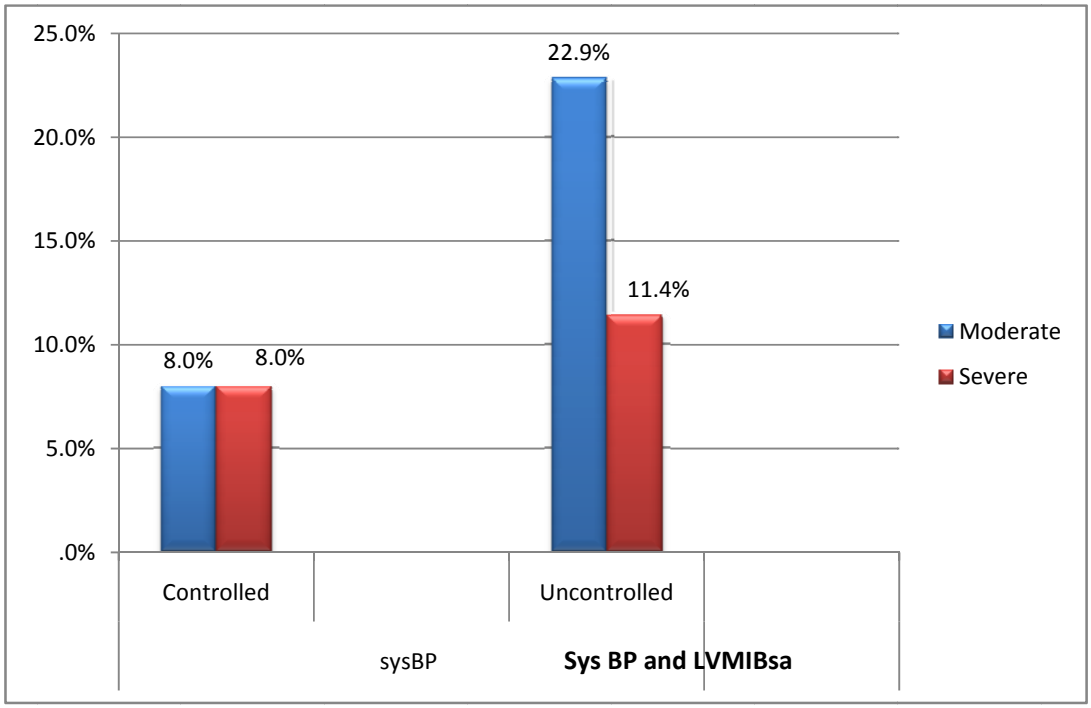

25.0%
20.0%
15.0%
10.0%
5.0%
.0%
22.9%
11.4%
8.0%
8.0%
Moderate
Severe
Controlled
Uncontrolled
sysBP
Sys BP and LVMIBsa

FIGURE - 8

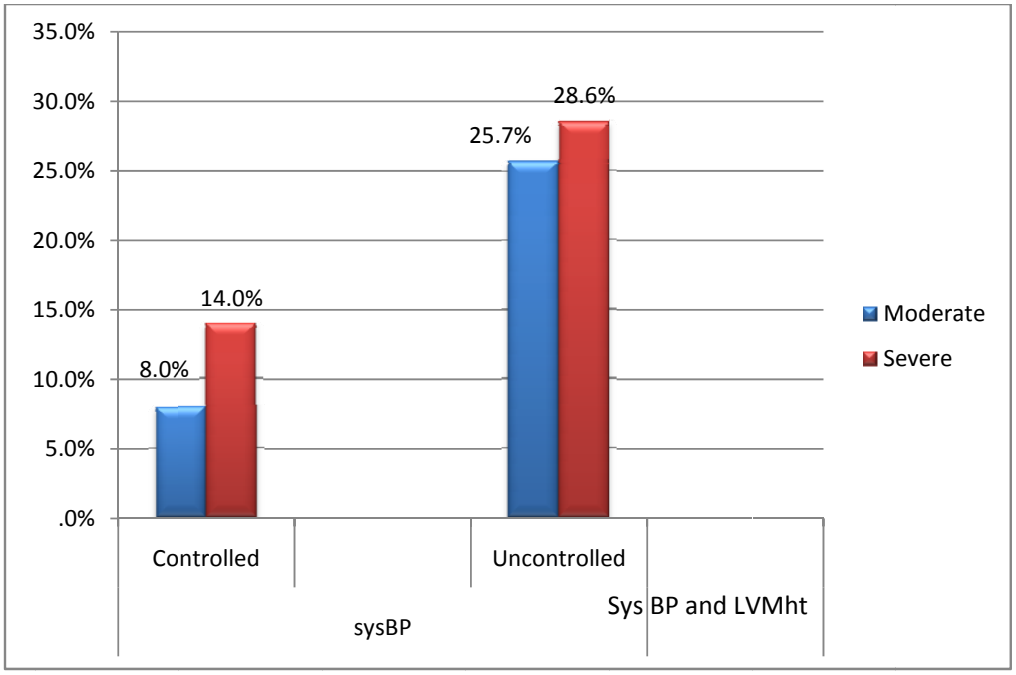

35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
.0%
8.0%
14.0%
25.7%
28.6%
Controlled
Uncontrolled
sysBP
Sys BP and LVMht
Moderate
Severe

FIGURE - 9

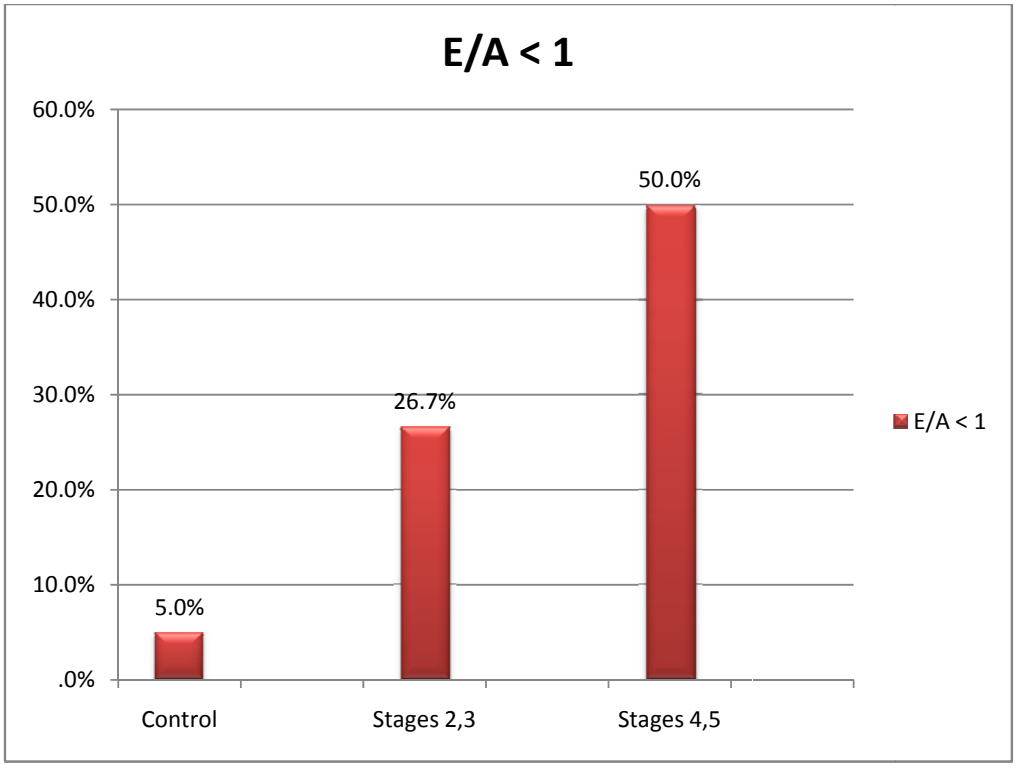

E/A < 1
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
.0%
5.0%
26.7%
50.0%
Control
Stages 2,3
Stages 4,5
E/A < 1

FIGURE - 10

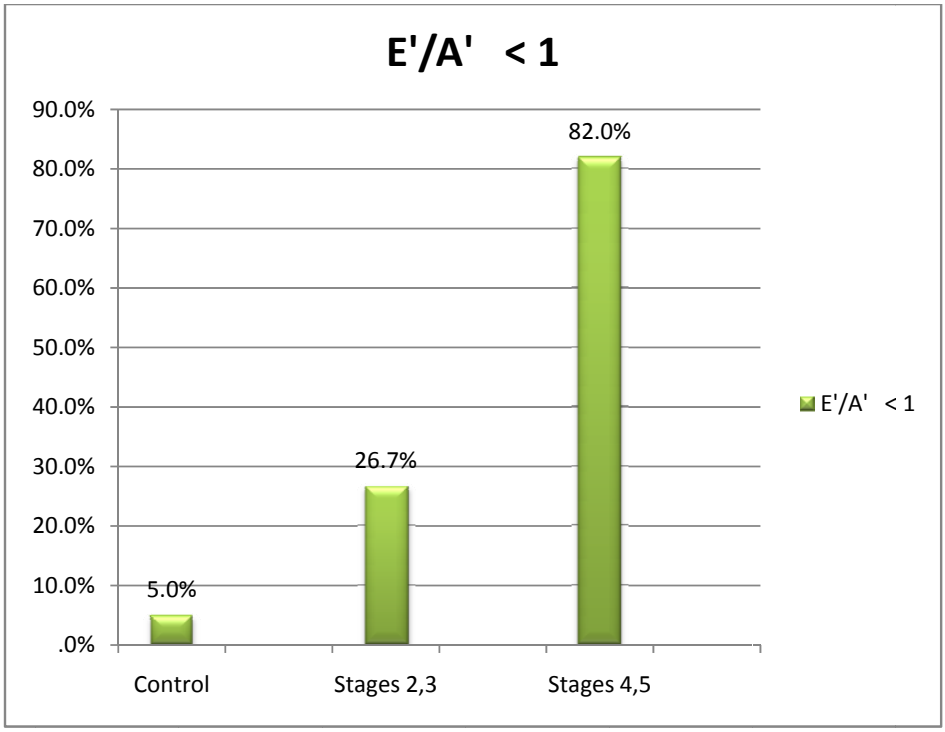

E'/A' < 1
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
.0%
5.0%
26.7%
82.0%
Control
Stages 2,3
Stages 4,5
E'/A' < 1

FIGURE - 11

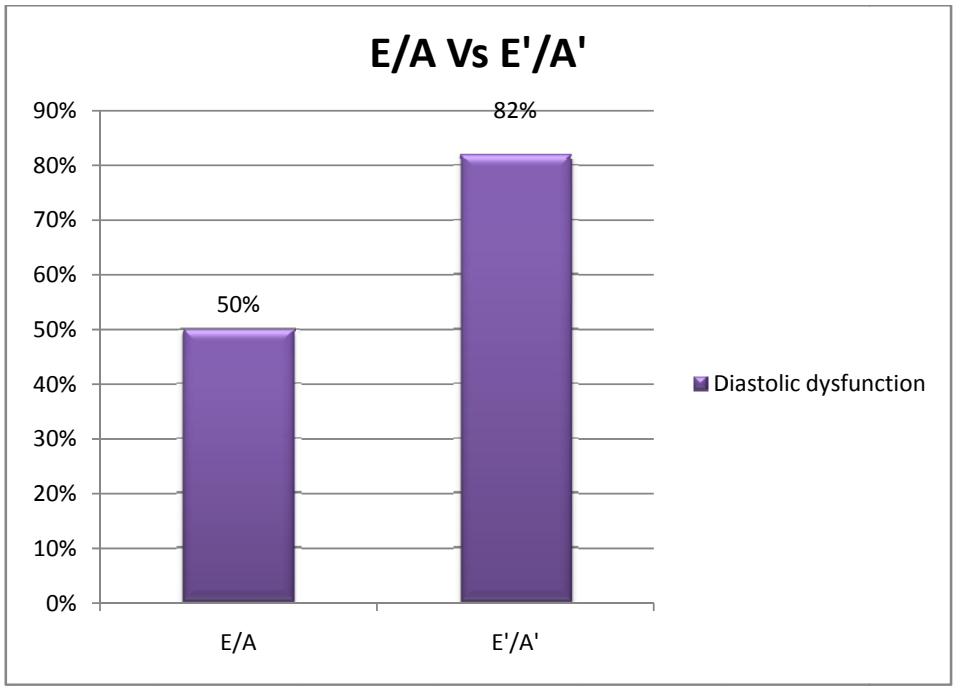
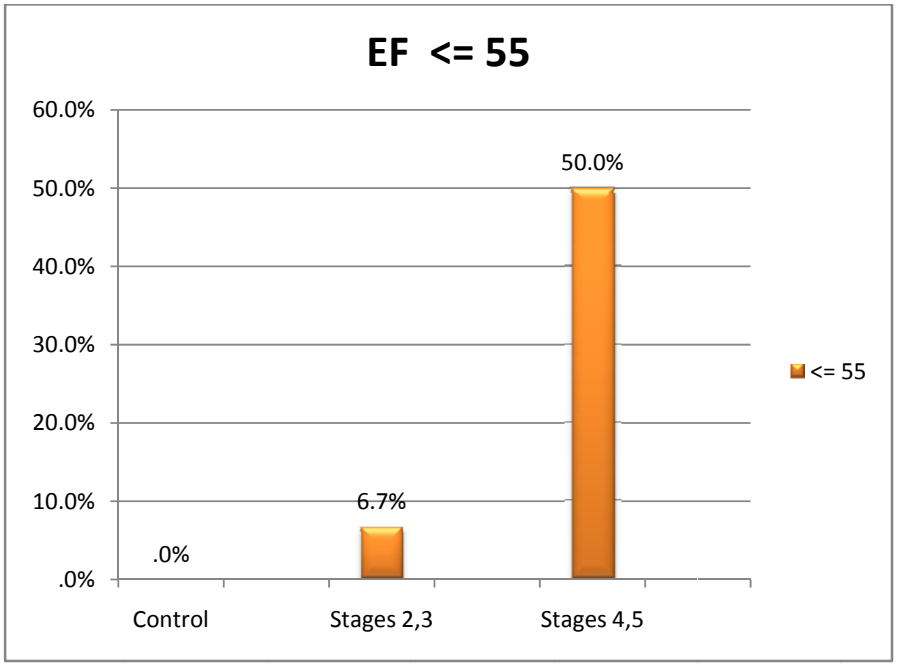


FIGURE - 12



BIBLIOGRAPHY

1. Rao M, Juneja R, Shirly RB, Jacob CK. Haemodialysis for end-stage renal disease in southern India--a perspective from a tertiary referral care centre. Nephrol Dial Transplant 1998; 13 : 2494-500.
2. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. Am J Kidney Dis 1994; 23 : 171-5.
3. Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease Charumathi Sabanayagam , Su Chi Lim , ,Jeannette Lee, Anoop Shankar and E Shyong Tai.
4. Hurtado A, Johnson RJ. Hygiene hypothesis and prevalence of glomernlonephritis. Kidney Int 2005; 97 (Suppl) : S62-7.
5. Mohan V, Deepa R. Adipocytokines and the expanding "Asian Indian Phenotype". J Assoc Physicians India 2006; 54 : 685-6.
6. Incidence of chronic kidney disease in India Suresh Chandra Dash and Sanjay K. Agarwal All India Institute of Medical Sciences, Nephrology, New Delhi, India.
7. Modified from National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation,

classification and stratification. Am J Kidney Dis 39:suppl 1, 2002.

8. Foley RN, Murray AM, Li S, et al: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005; 16(2):489-495.
9. London GM, Guerin AP, Marchais SJ: Hemodynamic overload in end-stage renal disease patients. *Semin Dial* 1999; 12:77-83.
10. London GM, Pannier B, Guerin AP, et al: Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: Follow-up of an interventional study. *J Am Soc Nephrol* 2001; 12(12):2759-2767.
11. Guerin AP, Blacher J, Pannier B, et al: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; 103(7):987-992.
12. Mazzaferro S, Coen G, Bandini S, et al: Role of ageing, chronic renal failure and dialysis in the calcification of the mitral annulus (abstract). *Nephrol Dial Transplant* 1993; 8:335-340.

13. London GM, Pannier B, Marchais SJ, Guerin AP: Calcification of the aortic valve in the dialyzed patient. *J Am Soc Nephrol* 2000; 11(4):778-783.

14. Otto CM, Lind BK, Kitzman DW, et al: Association of Aortic-Valve Sclerosis with Cardiovascular Mortality and Morbidity in the Elderly. *N Engl J Med* 1999; 341(3):142-147.

15. Levin A, Thompson CR, Ethier J, et al: Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34(1):125-134

16. Foley RN, Parfrey PS, Harnett JD, et al: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; 47(1):186-192.

17. Foley RN, Parfrey PS, Kent GM, et al: Long-term evolution of cardiomyopathy in dialysis patients. *Kidney Int* 1998; 54:1720-1725.

18. Takeda K, Nakamoto M, Baba M, et al: Echocardiographic evaluation in long-term continuous ambulatory peritoneal dialysis compared with hemodialysis patients. *Clin Nephrol* 1998; 49(5):308-312.

19. Enia G, Mallamaci F, Benedetto FA, et al: Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. *Nephrol Dial Transplant* 2001; 16(7):1459-1464.

20. Levy D, Garrison RJ, Savage DD, et al: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; 322(22):1561-1566.

21. Cheng W, Li B, Kajstura J, et al: Stretch-induced programmed myocyte cell death. *J Clin Invest* 1995; 96(5):2247-2259.

22. Katz AM: The cardiomyopathy of overload: An unnatural growth response in the hypertrophied heart. *Ann Intern Med* 1994; 121:262-371.

23. Mall G, Huther W, Schneider J, et al: Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrol Dial Transplant* 1990; 5(1):39-44.

24. Amann K, Ritz E: Cardiac disease in chronic uremia: Pathophysiology. *Adv Renal Replacement Ther* 1997; 4:212-224.

25. Weber KT, Brilla CG, Campbell SE, et al: Pathologic hypertrophy with fibrosis: The structural basis for myocardial failure. *Blood Pressure* 1992; 1(2):75-85

26. Amann K, Ritz E: Cardiac disease in chronic uremia: Pathophysiology. Adv Renal Replacement Ther 1997; 4:212-224.

27. Fujimoto S, Kagoshima T, Hashimoto T, et al: Left ventricular diastolic function in patients on maintenance dialysis: Comparison with hypertensive heart disease and hypertrophic cardiomyopathy. Clin Nephrol 1994; 42:109-116.

28. Barrett BJ, Parfrey PS, Morgan J, et al: Prediction of early death in end-stage renal disease patients starting dialysis. Am J Kidney Dis 1997; 29(2):214-222.

29. Parfrey PS, Harnett JD, Foley RN, et al: Impact of renal transplantation on uremic cardiomyopathy. *Transplantation* 1995; 60:908-914.

30. De Lima JJ, Vieira ML, Viviani LF, et al: Long-term impact of renal transplantation on carotid artery properties and on ventricular hypertrophy in end-stage renal failure patients. *Nephrol Dial Transplant* 2002; 17(4):645-651.

31. McGregor E, Stewart G, Rodger RS, Jardine AG: Early echocardiographic changes and survival following renal transplantation. *Nephrol Dial Transplant* 2000; 15(1):93-98.

32. Griselli M, Herbert J, Hutchinson WL, et al: C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. *J Exp Med* 1999; 190(12):1733-1740.

33. Torzewski M, Klouche M, Hock J, et al: Immunohistochemical demonstration of enzymatically modified human LDL and its colocalization with the terminal complement complex in the early atherosclerotic lesion. *Arterioscler Thrombosis Vasc Biol* 1998; 18(3):369-378.

34. Cermak J, Key NS, Bach RR, et al: C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993; 82(2):513-520.

35. Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men [erratum appears in N Engl J Med 337(5):356, 1997]. *N Engl J Med* 1997; 336(14):973-979.

36. Haverkate F, Thompson SG, Pyke SD, et al: Production of C-reactive protein and risk of coronary events in stable and

unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997; 349(9050):462-466.

37. Koenig W, Rothenbacher D, Hoffmeister A, et al: Infection with Helicobacter pylori is not a major independent risk factor for stable coronary heart disease: Lack of a role of cytotoxin-associated protein A-positive strains and absence of a systemic inflammatory response. *Circulation* 1999; 100(23):2326-2331.
38. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998; 97(20):2007-2011.
39. Panichi V, Migliori M, De Pietro S, et al: Plasma C-reactive protein in hemodialysis patients: A cross-sectional, longitudinal clinical survey. *Blood Pur* 2000; 18(1):30-36.
40. Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. *Am J Kidney Dis* 1997; 29(5):658-668.
41. Libetta C, De Nicola L, Rampino T, et al: Inflammatory effects of peritoneal dialysis: Evidence of systemic monocyte activation. *Kidney Int* 1996; 49(2):506-511.

42. Yeun JY, Levine RA, Mantadilok V, Kaysen GA: C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000; 35(3):469-476.

43. Zoccali C, Benedetto FA, Maas R, et al: CREED Investigators. Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol* 2002; 13(2):490-496.

44. Stenvinkel P, Heimburger O, Paultre F, et al: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999; 55(5):1899-1911.

45. London GM, Guerin AP, Marchais SJ, et al: Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant 2003; 18(9):1731-1740.

46. Ribeiro S, Ramos A, Brandao A, et al: Cardiac valve calcification in haemodialysis patients: Role of calcium-phosphate metabolism. *Nephrol Dial Transplant* 1998; 13(8):2037-2040.

47. Mazzaferro S, Coen G, Bandini S, et al: Role of ageing, chronic renal failure and dialysis in the calcification of the mitral annulus (abstract). *Nephrol Dial Transplant* 1993; 8:335-340.

48. Ribeiro S, Ramos A, Brandao A, et al: Cardiac valve calcification in haemodialysis patients: Role of calcium-phosphate metabolism. *Nephrol Dial Transplant* 1998; 13(8):2037-2040.

49. Braun J, Oldendorf M, Moshage W, et al: Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996; 27(3):394-401.

50. Rosenhek R, Binder T, Porenta G, et al: Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000; 343(9):611-617.

51. *Hypertension Research* (2008) 913–920; doi:10.1291 /hypres.31.913. Presence of Chronic Kidney Disease and Subsequent Changes of Left Ventricular Geometry over 4 Years in an Apparently Healthy Population Aged 60 and Older. Ya-Ting Lee, Herng-Chia Chiu, Ho-Ming Su, Wen-Chol Voon, Tsung-Hsien Lin, Wen-Ter Lai and Sheng-Hsiung Sheu

52. 52.Locatelli F, Pozzoni P, Del Vecchio L. Recom-binant human epoetin beta in the treatment of renal anemia. Ther Clin Risk Manag 2007;3 (3):433-9.

53. Afshar R, Sanavi S, Salimi J, Ahmadzadeh M. Hematological profile of chronic kidney disease (CKD) patients in Iran, in pre-dialysis stages and after initiation of hemodialysis. Saudi J Kidney Dis Transpl 2010;21:368-71.

54. J Assoc Physicians India. 2006 Sep;54:699-703.Correlation of anemia, secondary hyperparathyroidism with left ventricular hypertrophy in Chronic Kidney Disease patients.Datta S, Abraham G, Mathew M, Somasundaram H, Muralidharan TR, Moorthy A, Sathyasekaran, Leslie N. Department of Medicine, Madras Medical Mission, Chennai.

55. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-1305.

56. Foley RN, Parfrey PS, Kent GM et al. Long-term evolution of cardiomyopathy in dialysis patients. Kidney Int 1998; 54: 1720-1725.

57. Amann K, Wanner C, Ritz E. Cross-talk between the kidney and the cardiovascular system. J Am Soc Nephrol 2006; 17: 2112-2119.

58. Amann K, Tyralla K, Gross ML et al. Cardiomyocyte loss in experimental renal failure: prevention by ramipril. Kidney Int 2003; 63: 1708-1713

59. Tillett WS, Francis T: Serological reaction in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med 52: 561–571, 1930.

60. Inflammatory Marker Mania in Chronic Kidney Disease: Pentraxins at the Crossroad of Universal Soldiers of Inflammation Kamyar Kalantar-Zadeh

61. Harold Simmons Center for Kidney Disease Research and Epidemiology, Los Angeles Biomedical Research institute at Harbor-UCLA Medical Center, and David Geffen School of Medicine at UCLA, Torrance, California Clin J Am Soc Nephrol 2: 872-875, 2007. doi: 10.2215/CJN.02750707.

62. Lipid profile in pre-dialysis chronic kidney disease patients attending University of Maiduguri Teaching Hospital, Maiduguri-Nigeria. Mshelia DS, Buratai LB, Mamza YP. Department of Chemical Pathology, University of Maiduguri, Nigeria.

63. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003;41(4 Suppl):I-IV,S1-S91.

64. Foley RN, Parfrey PS, Harnett JD, et al: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 1996; 7(5):728-736.

65. Rigatto C, Parfrey P, Foley R, et al: Congestive heart failure in renal transplant recipients: Risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol* 2002; 13:1084-1090.

66. Parfrey PS, Foley RN, Harnett JD, et al: Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; 11(7):1277-1285.

67. Rigatto C, Foley RN, Kent GM, et al: Long-term changes in left ventricular hypertrophy after renal transplantation. *Transplantation* 2000; 70(4):570-575.

68.. Harnett JD, Foley RN, Kent GM, et al: Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis, and risk factors. *Kidney Int* 1995; 47:884-890.

69. Suega K, Bakta M, Dharmayudha TG, Lukman JS, Suwitra K. Profile of anemia in chronic renal failure patients. Acta Med Indones (serial online) 2005;37(4):190-4.

70. Fernandez-Rodriguez AM, Guindeo-Casasus MC, Molero-Labarta T. Diagnosis of iron deficiency in chronic renal failure. Am J Kidney Dis 1999; 34:508.

71. Wallach J. Interpretation of Diagnostic Tests. 7th ed, Boston, Little Brown, 2000;3: 57.

72. Raji D, Dominic E, PaI A. Skeletal muscle, cyto-kines and oxidative stress in ESRD. Kidney Int 2005;68:2338-44.

73. 73. Echocardiographic assessment of left ventricular hypertrophy in patients of chronic renal failure P Dangri*, S Agarwal**, OP Kalra***, S Rajpal*****Postgraduate Student, **Reader, ***Professor, ****Medical Specialist,Department of Medicine, University College of Medical Sciences & GTB Hospital, Delhi Indian J Nephrol 2003;13: 92-97

74. Adewole A Adebiyi,[1] Okechukwu S Ogah,[2] Akinyemi Aje,[2] Dike B Ojji,[2] Adedeji K Adebayo,[2] Olulola O Oladapo,[1] and Ayodele O Falase[1]

75. [1]Division of Cardiovascular Medicine, Department of Medicine, University College Hospital, Ibadan, PMB 5116 Ibadan, Oyo

State, Nigeria/Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Ibadan, Nigeria Echocardiographic partition values and prevalence of left ventricular hypertrophy in hypertensive Nigerians.

76. de Simone G, Kizer JR, Chinali M, Roman MJ, Bella JN, Best LG, Lee ET, Devereux RB. Normalization for body size and population-attributable risk of left ventricular hypertrophy: the Strong Heart Study. *Am J Hypertens.* 2005;191–196. doi: 10.1016/j.amjhyper.2004.08.032.

77. Shirley Yumi Hayashi, Morteza Rohani, Bengt Lindholm, Lars-Åke Brodin ,Britta Lind, Peter Barany, Anders Alvestrand Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging.

78. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916; 17:863-71.

79. Wang Y, Moss J, Thisted R. Predictors of body surface area. J Clin Anesth. 1992; 4(1):4-10.